Editorials

N-of-1 Randomized Trials—Where Do We Stand?

RANDOMIZED CLINICAL TRIALS in individual subjects (N-of-1 RCTs), described in detail elsewhere in this issue by Eric Larson, are old to psychology but new to clinical medicine. Ironically enough, physicians, in comparison to clinical psychologists, are at a considerable advantage in conducting N-of-1 RCTs. Psychologists are usually evaluating behavioral therapies that cannot be masked and are likely to be subject to carryover effects. For physicians, N-of-1 RCTs are generally used to assess drug therapy that often acts, and ceases to act, quickly and for which full double-masking can be undertaken. Nevertheless, psychologists' 30-year experience compares with the less than 3 years in which physicians have been using N-of-1 RCTs in an intensive way. As a result, there are many questions about the technique that remain to be answered.

As described by Larson, N-of-1 RCTs generally consist of a series of pairs of treatment periods, with each pair including one period on active or experimental medication and one period on placebo or alternative. The order of the active and placebo medication within pairs is determined by random allocation. Treatment targets (a laboratory measurement, physical sign, or [most often] patient symptoms) are monitored throughout the trial. Differences between active and placebo periods can be evaluated by intuition, examining graphic representations, or formal statistical analysis.

The first set of questions concerning N-of-1 RCTs that remains to be answered has to do with the optimal method of conducting N-of-1 RCTs. Larson, for instance, suggests that statistical power can be gained by abandoning the usual approach of paired treatment periods and using unconstrained randomization. Using unconstrained randomization permits the possibility of, for instance, six treatment periods being ordered so that the first three all use placebo and the last three use active treatment. Our bias is that when studying individual patients, there is an excessive risk that steady improvement or deterioration, or the occurrence of a single exacerbating or ameliorating event at the point where placebo and an active agent switch, could invalidate the results of a design using unconstrained randomization. Experience using both approaches will, however, be required to determine whether or not our concerns are justified.

A second methodologic issue concerns the statistical analysis of N-of-1 RCTs. Larson refers only to nonparametric methods. These are limited in that they do not take into account the magnitude of differences between active and placebo periods in determining how likely the results were to have occurred by chance. We think that more powerful conventional parametric techniques can be applied to the analysis of N-of-1 RCTs.[1] Other practical issues in doing N-of-1 RCTs include the best way of measuring symptoms, the interpretation of symptom measurement,[2] the optimal trade-off between the length and the number of treatment periods, and the importance of statistical analysis in interpreting the results. While we have our opinions on these issues,[1] they will ideally be explored by investigators interested in N-of-1 methodology.

A second set of questions concerning N-of-1 RCTs has to do with how practical and useful they will prove in clinical practice. Larson reports our initial experience with 42 N-of-1 RCTs. Subsequent trials have continued to demonstrate the ability of the method to resolve difficult clinical dilemmas and the fact that, based on the results, treatment frequently changes.[3] This does not establish, however, whether physicians will continue to rely on open, unmasked, before and after studies, the usual way of conducting clinical practice. While traditional approaches have all the limitations that Larson points out, they have one major advantage: they are easy. N-of-1 RCTs require additional time, effort, and thought that a busy clinician may be reluctant to invest. We have received many inquiries about N-of-1 RCTs but few reports back as to how successful individual experiments, or plans for N-of-1 services, have been. Our results with the technique show that N-of-1 RCTs can result in a more appropriate use of medication and improved clinical care[3]; it will be intriguing to see the extent to which widespread application of the approach occurs.

A final set of questions concerning N-of-1 RCTs has to do with their application in the investigative, rather than the clinical practice, setting, particularly in the development of new drugs. Currently the drug development process is characterized by the commencement of large-scale randomized trials at a point where crucial questions remain unanswered. These include the likely magnitude of the treatment effect, the optimal dose of the medication, the most responsive subgroup(s), and the extent of the heterogeneity of treatment response. A small series of N-of-1 RCTs could be extremely useful in resolving these issues and lead to a much more efficient drug development process. We are currently exploring this question in the testing of a new nootropic agent for senile dementia and are trying to interest other pharmaceutical companies in the use of N-of-1 RCTs.

In these efforts, we have seldom been so bold as to suggest that N-of-1 RCTs could be used in the definitive phases of new drug testing. When we have, the suggestion has been viewed with (perhaps appropriate) skepticism, but we think it is worthy of consideration. Conventional RCTs tell us the average magnitude of an effect in a population. Clinicians treat individual patients, however, not populations. A large series of N-of-1 RCTs could tell a clinician about the number of patients who are likely to respond, the common magnitude of the response, the heterogeneity of the response, and the patient characteristics that predict response. These questions are of primary interest to clinicians. While we do not deny that conventional parallel group RCTs can elucidate these issues to some extent, a large series of N-of-1 RCTs would do better.

The N-of-1 RCTs approach that Larson describes has tremendous potential. We will likely see, in the next decade, the extent to which this potential is realized.

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Are Vitamin A Supplements Needed During Pregnancy?

THE INTRODUCTION of therapeutic retinoids in the 1980s for the treatment of severe acne and psoriasis led to initial claims that these were "miracle" drugs. Within several years of their approval for marketing, however, it became clear that these retinoids posed an unusually high risk for adverse outcomes of pregnancy when taken after conception. The unusual magnitude of this teratogenic risk, coupled with the fact that vitamin A (retinol) was known to induce identical malformations in an experimental setting, has prompted reasonable concerns that supplementation with retinol during pregnancy may be hazardous to developing embryos and fetuses.

This concern will be heightened if experimental studies find that the teratogenic properties of retinol are largely mediated by its metabolic conversion to retinoic acid. This has not been conclusively demonstrated yet, and it is unclear whether retinol induces malformations independently.[1] There are several important pharmacokinetic differences between retinol and retinoic acid that probably act to reduce the potential for human retinol teratogenicity.[2] First, the intake of retinol, in contrast to that of retinoic acid, is necessary for human health, and so a sophisticated system has evolved to maintain body storage and to regulate the serum concentration available to other tissues. Retinol is stored in liver cells and is bound in serum by a specific carrier protein, retinol-binding protein. Excess absorbed retinol is rapidly removed from the serum and stored. Retinoic acid, on the other hand, is not stored and is nonspecifically bound to serum albumin. These different properties make it less likely that excess vitamin A intake might be teratogenic compared with retinoic acid. It is unknown whether excess retinol intake might substantially increase serum levels of all-*trans*-retinoic acid.

Although concerns about the possible teratogenicity of vitamin A are reasonable, there are no systematically conducted human studies to quantitate this risk. Werler recently found a twofold increased risk for vitamin A supplementation and malformation of structures that are composed, at least in part, from cranial neural crest cells.[3] This cell population has been shown to be susceptible to retinoic acid exposure in utero. Werler's study found that 0.2% of control mothers took a vitamin A supplement during early pregnancy. Other surveys have shown geographic variations in vitamin A supplementation but generally have found that less than 0.5% of nonpregnant women of reproductive age take vitamin A supplements of 25,000 IU per day or more. Given this low frequency of supplementation, it will be difficult to identify small increased risks for major malformations in human studies.

The recommendations of Kizer and associates and the Teratology Society to limit the maximum amount of vitamin A per unit dose are sensible and should be implemented. I do not agree that an increased need has been found for vitamin A during pregnancy that requires supplementation. Like most of the components of vitamin supplements taken during pregnancy, vitamin A has traditionally been included in the supplement without any evidence that the usual dietary intake is inadequate and without any evidence that supplementation in developed countries is beneficial to mother or fetus. In developed countries, there appears to be little or no scientific basis for supplementing pregnant women with retinol or retinyl esters, while there is a small possibility of causing harm. It makes sense that vitamin supplements taken prenatally, if they contain vitamin A at all, ought to include only β-carotene as the source of vitamin A. An argument can easily be made that this logic holds for using β-carotene as the source of vitamin A for all commercially available supplements. Regulatory agencies should work with manufacturers to bring about such changes.

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Health Care—Where Are the Problems and Where Are the Solutions?

THE BASIC PROBLEMS in what we call health care are problems for the patient, the family, and, to a greater or lesser extent, the immediate health care environment of an ill person. The problems are actually problems of illness rather than of health, and the first and most important steps in health care have to be taken where the sick, injured, or emotionally disturbed person is, with the resources for care that are available. This is what health care is all about. Yet there are many who view it differently. They see it more as a national problem that, therefore, requires a national solution, by which they mean a nationalized system for rendering patient care. This view is reinforced by the rising cost of health care, which is now nationwide and has become a problem not only for the persons afflicted, their families, and the immediate community, but for business and industry and even for government at the local, state, and national levels. For some time we as a nation have been wont to turn to government when things need to be done that are beyond the reach of individuals or local communities. Government can spread the costs over a wider base, and this substantially reduces personal responsibility for them. The pain of the cost is softened until tax time, and even then it is more often directed toward the amount of the tax, with little consideration of the value of the benefits that in most cases seem to accrue to someone else.

But the fact is the problems of health care and its costs affect almost everyone. They can be viewed as personal, community, local, state, and national problems. For a while there was considerable enthusiasm for a comprehensive, all inclusive program of national health insurance to be administered and paid for by government. As costs have risen, enthusiasm for this has cooled. Actually, a trend quite the opposite has begun to develop. Among the myriads of health care plans and programs that have come into being in business and industry and in government at all levels, there is a notable tendency to push responsibility for paying the costs down-